

Course BB2170

Drug Development



Veronique Chotteau (responsible), Amelie Eriksson Karlström (examiner)
School of Engineering Sciences in Chemistry, Biotechnology, and Health, KTH



Veronique Chotteau

- PhD Biotechnology/Automatic Control (Univ Louvain, Belgium)
- 1996 - 2008 → Pharmacia-Upjohn / BIOVITRUM
 - Senior Project manager – Development of manufacturing process for biopharmaceutical production
- From 2008 → Cell Technology group, Industrial Biotechnology Dept., CBH School
 - Development of process for the production of biopharmaceuticals with mammalian/human cells
 - High cell density continuous bioprocessing
 - Mathematical modelling of metabolism, glycosylation
 - Bioprocessing for cell therapy and viral vector manufacturing
 - Director of AdBIOPRO – Competence Centre for Advanced Bioproduction by Continuous Processing – Lund University, Karolinska Hospital/Institute, Sobi, GE Healthcare, Cobra Biologics, BioInvent, Valneva, CellProtect, LOAB
 - Coordinator of iConsensus project, EU, IMI2 – Sanofi, Bayer, Pfizer, GSK, Rentschler, Synthon, UCB, Mons University, Hohenheim Univ, RWTH-Aachen, m2p, Presens, Micronit, Ipratech, Iprasens, PaiaBio, Kantisto, Svanholm
 - Part of Wallenberg Centre for Protein Research with MedImmune, AstraZeneca
 - Part of CAMP, Centre for Advanced Medical Products
 - Part of STACCATO, EU, Marie-Curie

1. Register for the course NOW!
2. Register for the examination in good time!
3. Communication about the course with me
→ chotteau@kth.se
→ mention **BB2170** in email subject

Aims of the course

After the course you should be able to describe and discuss the **different stages** in the process of drug development.

- identify important **differences between different classes of drug substances** (proteins vs. small, organic molecules) with respect to pharmacodynamics, pharmacokinetics, production, safety and therapeutic areas
- make an analysis of the **commercial landscape** of therapeutic drugs, state which are the **commercially important therapeutic areas**
- define important **concepts** within drug discovery and drug development, state which types of studies are used in the process of drug development, and describe which **strategies / methods** are employed in the different steps
- explain what are drug **administration, absorption, distribution and elimination**, and how these impact the dosing of drugs

Aims of the course – in short!

After the course you should

- have an understanding of actual medicine drugs (effects, interaction with the body, manufacturing, market)
- be able to describe, discuss and analyze the process of drug discovery and development
 - from discovery of the drug to the patient

Why do we want to study drug development?

- New medicinal drugs for unmet medical needs
- Complex action/interaction in/on the body → need to understand the biology and chemistry
- Medicinal drugs have always side effects
- The business aspects of the pharmaceutical industry
- Important job market for biotechnology and chemistry students
- Research

Course Memo

Prerequisites (recommended)

Chemistry and biology!

BB1010 Introduction to Biotechnology
BB1020 Cell Biology with Immunology
KD1090 Organic Chemistry I
BB1090 Biochemistry
... or equivalent

Language

All lectures and project discussions will be held in English

Course Memo

Lectures

20 lectures

17 invited specialists from industry (13) / academia (4)

Course web page

KTH Social and CANVAS (available for registered students)

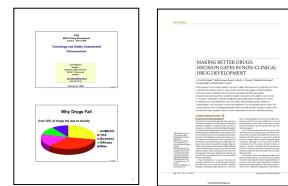
Project

Literature project presented by a written report (individually) and an oral presentation (in group) during one seminar day – **Compulsory** attendance the seminar day

Literature

Handouts

Review articles and book chapters - a list will be provided (available on KTH Social)



Project (group of ≈ 4 persons)

Subject = two drugs of different types

Target and molecular mechanism

- What are the underlying **mechanisms of the disease** and of the **treatment** brought by the drugs?
- What is/are the **target(s)** for the drugs?
- How are the drugs **reaching their target**?
- How the disease and the action of the drugs have been or can be studied in **animal models** (which model(s)?), or **other** types of **model** studies such as cell-based assays, etc. (which study/ies?).
- Discuss the **bioavailability** of the drugs.
- What is the efficacy of the drugs, incl. **dose effect, EC50** (or IC50 if more adequate)?

Drug substance

- Are the drugs **small molecule or protein**?
- What are the **production processes** of the drugs?
- How are the **drugs administered**, including **frequency**? Motivate the administration choice.
- What are the **half-life, t_{1/2}**, of the drugs? Discuss the half-life in relation with the treatment.
- Describe the **metabolism** of the drugs (in particular for small molecule drugs) and how are drugs **eliminated** from the body.
- In general, there are typical **advantages** and **disadvantages** of **small molecule** drugs versus **biopharmaceuticals**. Reflect on how these advantages and disadvantages apply to the drugs of your project?

.../...

Project

Risk/benefit analysis

- What are the known **side effects** of the drugs?
- How are the frequency and severity of the side effects compare with the desired effects of the drugs? Do a **risk contra benefit** analysis.
- Present briefly the **clinical trials** for phase I, IIa, IIb, III: what was the number of patients, which patients were enrolled, what were the purpose and the outcome.
- For this particular disease, what seems to be the **best drug** among the two studied?

IPR/marketing

- Are the drugs covered by **patent(s)**?
- Are there any **generic** versions of the drugs on the market?
- What are the **competitors** for the indication of the studied drugs? Looking at all the **existing drugs** for this indication, what seems to be the best option for this disease? How is the **market share** of the different existing drugs for this indication, and in particular of drug A and B?

Project

Contact: chotteau@kth.se

Project

- Attribution of different drugs to the groups
 - groups → email **dead line Sept 1** → chotteau@kth.se with **name** and **email**
 - either of - already formed group or
 - individual registration → will be assigned in a group

- Material for the project
 - Material given in the lectures and
 - Own research from literature and internet

mention **BB2170**
in email subject

- Individual** reports
 - Address all the different items (summary and analysis of collected information/ data)
 - No copy/paste of literature or internet → number of direct citations from literature or internet limited to two (indicated with ' ')
 - Screened for plagiarism

Peer-review of reports

Presentation by groups including opposition (different from opposition) → **compulsory**

- Friday Oct 12 08:00-17:00 AlbaNova FB51

Examination and grading

Examination

Written examination

Week 43 - Fri 26 oct 14:00-19:00 - FB52, FB53 at AlbaNova.

Short questions + questions requiring longer development

Registration required!

Grading

The project: report, peer reviewing, presentation, opposition → pass/fail with bonus for very good work

Screening for plagiarism - no bonus if high score of plagiarism

The written examination → graded

The final grade of the course is based on the results of the written examination and takes into account the bonus given for the project work

Outline of Today's Lecture

- A brief history of the therapeutic drugs
- Trends in the pharmaceutical industry
- The process of drug discovery and development
- Regulation of drug development



Short history of the Pharmaceutical Drugs

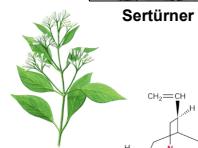
- Plants used since...
- Paracelsus (16th century): Proposed that herbs, plant extracts, etc used in medicine contain an **active ingredient**. Used chemicals (inorganic salts) as medicines. Considered the "father of toxicology".
- Sertürner (1806): Isolation of pure **morphine** from opium, which led to the search and discovery of other alkaloids in plants in 1820-1840.
- Gerhardt (1853): synthesis of **aspirin** (acetylsalicylic acid)
- Pelletier & Caventou (1826): Establishment of the first "modern" **pharmaceutical company**, producing quinine (for treatment of fever) from cinchona bark.
- Knorr & Filehne (1884): First **synthetic drug**: Antipyrin (phenazone), a fever-reducing drug, sold by Hoechst
- Commercialisation of **Aspirin** (1893) by Hoffman (Bayer)



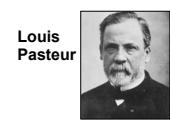
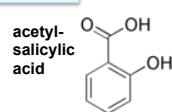
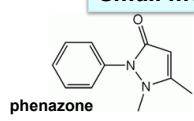
Paracelsus



Sertürner



Small molecules

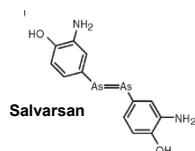


Louis Pasteur

Source: Pharmaceutical Innovation (1999) Chemical Heritage Press

Short history of the Pharmaceutical Drugs

- Paul Ehrlich (1854-1915): Described many new concepts for drug development:
 - **experimental therapy** (the use of laboratory animals as disease models)
 - **chemotherapy** (screening chemicals to identify drug substances)
 - **the “magic bullet”** (a specific drug substance targeting a specific disease/molecule)
 - **immunology**



from: <http://nobelprize.org>



from: bbc.com

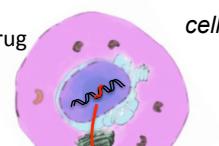
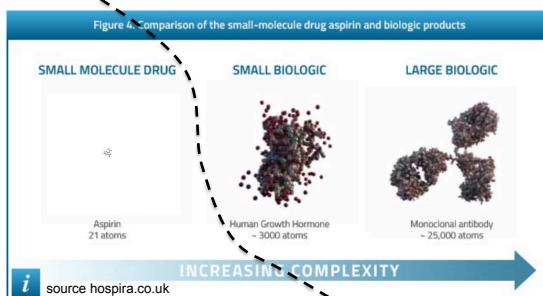
- (1961): The **thalidomide** tragedy. The sedative drug thalidomide (brand name: "Neurosedyn" in Sweden) led to the birth of thousands of deformed babies after prescription to pregnant women.

→ This tragedy led to stricter control of the approval of new drugs, more extensive clinical trials and longer development times.

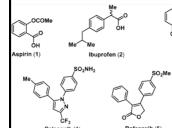
Small molecules and biopharmaceuticals

Biopharmaceutical

- large molecule biologically active used as medical drug
- most often protein (e.g. antibody)



protein
20000 to 250000 g/mol

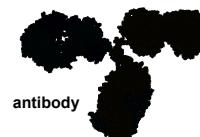
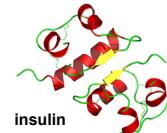


- Small molecule**
- organic synthesis
- 200 to 600 g/mol



Short History of Biotechnological Drugs

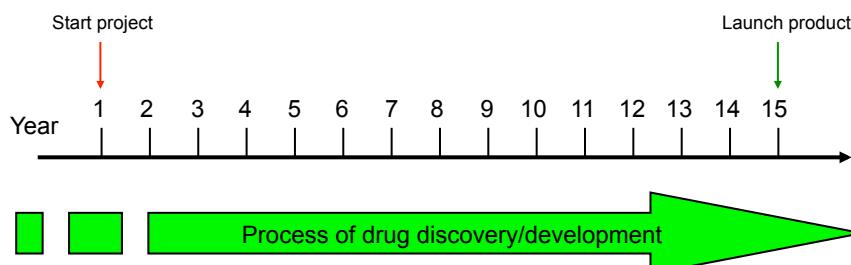
- Banting & Best (1921): discovery of **insulin** for treatment of diabetes, soon isolated and sold by Lilly.
- (1970s): Development of **recombinant DNA technologies**
- (1982): First product of recombinant DNA technology: recombinant human insulin launched by Lilly/Genentech – E.coli
- (1985): Recombinant human growth hormone launched by Genentech
- (1986): First **monoclonal antibody** approved for use in human: Orthoclone OKT3 (muromonab-CD3) developed by Ortho Biotech for prevention of transplant rejection.
- (1987): Recombinant tissue plasminogen activator (tPa) – First recombinant DNA mammalian cell-based process → CHO cells
- (1997): First **recombinant (chimeric) antibody** approved for cancer therapy: Rituxan (rituximab) developed by Genentech, Hoffmann-La Roche and Biogen Idec Inc.



Biopharmaceuticals

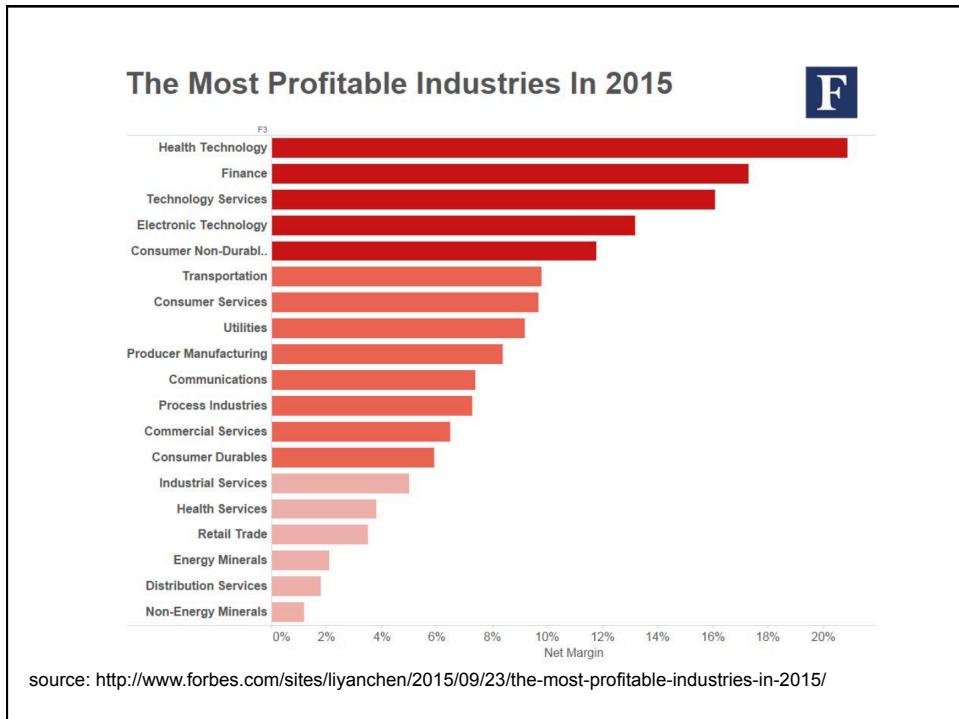
Source: Biotechmedia

Towards a New Drug – Some Figures



The development of a new drug...

- takes 10-15 years
- costs US \$ 500-4000 million, average 1380 (2011) – 138 (1975)
- ~ 20-30 new drugs are introduced each year
- The global sales of prescription drugs was more than US \$ 800 billion in 2009 (Source: IMS Health 2009)
- expected US \$ 1,200 billion by 2016 (source IPFMA 2011)
new chemical or biological entities (NCEs and NBEs)



Top 20 Pharmaceutical Industries

#	Company	2014 (\$m)	2013 (\$m)	
1	Novartis	47101	47468	Based on sales of prescription medicines, including generics drugs
2	Pfizer	45708	47878	
3	Roche	39120	39163	
4	Sanofi	36437	37124	
5	Merck & Co.	36042	37437	
6	Johnson & Johnson	32313	28125	
7	GlaxoSmithKline	29580	33330	
8	AstraZeneca	26095	25711	
9	Gilead Sciences	24474	10804	
10	Takeda	20446	19158	
11	AbbVie		20207	
12	Amgen		19327	
13	Teva		18374	
14	Lilly		17266	
15	Bristol-Myers Squibb		15879	
16	Bayer		15486	
17	Novo Nordisk		15329	
18	Astellas		14099	
19	Boehringer Ingelheim		13830	
20	Actavis		13062	

Source: http://www.pmlive.com/top_pharma_list/global_revenues

Top 20 Pharmaceutical Industries

#	Company		2014 (\$m)	2013 (\$m)	
1	Novartis	Switz.	47101	47468	Based on sales of prescription medicines, including generics drugs
2	Pfizer	USA	45708	47878	
3	Roche	Switz.	39120	39163	
4	Sanofi	France	36437	37124	
5	Merck & Co.	USA	36042	37437	
6	Johnson & Johnson	USA	32313	28125	
7	GlaxoSmithKline	UK	29580	33330	
8	AstraZeneca	UK-Sweden	26095	25711	
9	Gilead Sciences	USA	24474	10804	
10	Takeda	Japan	20446	19158	
11	AbbVie	USA	20207		
12	Amgen	USA	19327		
13	Teva	Israel	18374		
14	Lilly	USA	17266		
15	Bristol-Myers Squibb	USA	15879		
16	Bayer	Germany	15486		
17	Novo Nordisk	Denmark	15329		
18	Astellas	Japan	14099		
19	Boehringer Ingelheim	Germany	13830		
20	Actavis	USA	13062		

Source: http://www.pmlive.com/top_pharma_list/global_revenues

US-Canada, Europe, Japan are dominating

Global purchase of prescribed drugs

	2005	2015 (expected)
US	41%	31%
Europe	27%	19%
Leading emerging countries	12 %	28%

Top 10 Best Selling Drugs in the world in 2014

Top 10 drugs 2014 sales (\$m)					
	Brand	Indication	Company	2014 sales (\$m)	2020 sales (\$m)
1	Humira	Autoimmune (various)	AbbVie	12543	14780
2	Sovaldi	Hepatitis C	Gilead	10283	16621
3	Remicade	Autoimmune (various)	J&J/Merck & Co.	9240	7601
4	Enbrel	Autoimmune (various)	Amgen/Pfizer	8538	7754
5	Lantus	Diabetes	Sanofi	8433	5497
6	Rituxan	Leukaemia/lymphoma	Roche	7550	5486
7	Avastin	Cancer (various)	Roche	7021	6480
8	Advair	Asthma/COPD	GSK	6971	2582
9	Herceptin	HER2+ breast cancer	Roche	6866	4573
10	Januvia	Diabetes	Merck & Co.	6002	9187

Source: Company reported data; Bloomberg

Biopharmaceuticals	
Small molecules	http://www.firstwordpharma.com/node/1263906#axzz3qXSmCs2y

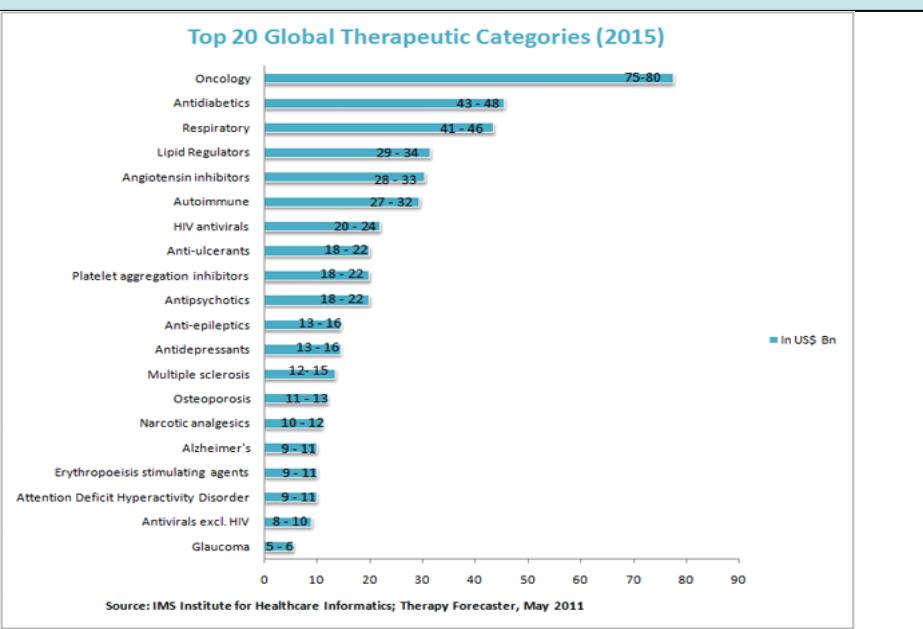
Top 12 Best Selling Drugs in USA in 2011

Trade name	Company	Sales (US \$ billion)
1. Lipitor	Pfizer	7.7
2. Plavix	Bristol-Myers Squibb / Sanofi-Aventis	6.8
3. Nexium	AstraZeneca	6.2
4. Abilify	Otsuka / Bristol-Myers Squibb	5.2
5. Advair Diskus	Glaxo SmithKline	4.6
6. Seroquel	AstraZeneca	4.6
7. Singulair	Merck	4.6
8. Crestor	Shionogi / AstraZeneca	4.4
9. Cymbalta	Eli Lilly	3.7
10. Humira	Abbott	3.5
11. Enbrel	Amgen /Wyeth	3.5
12. Remicade	Centocor / Schering-Plough /Janssen	3.5

"The patent cliff"

(The top-selling US prescription drugs in 2011, from IMS Health)

Top 10 Therapeutic classes globally



Orphan drug

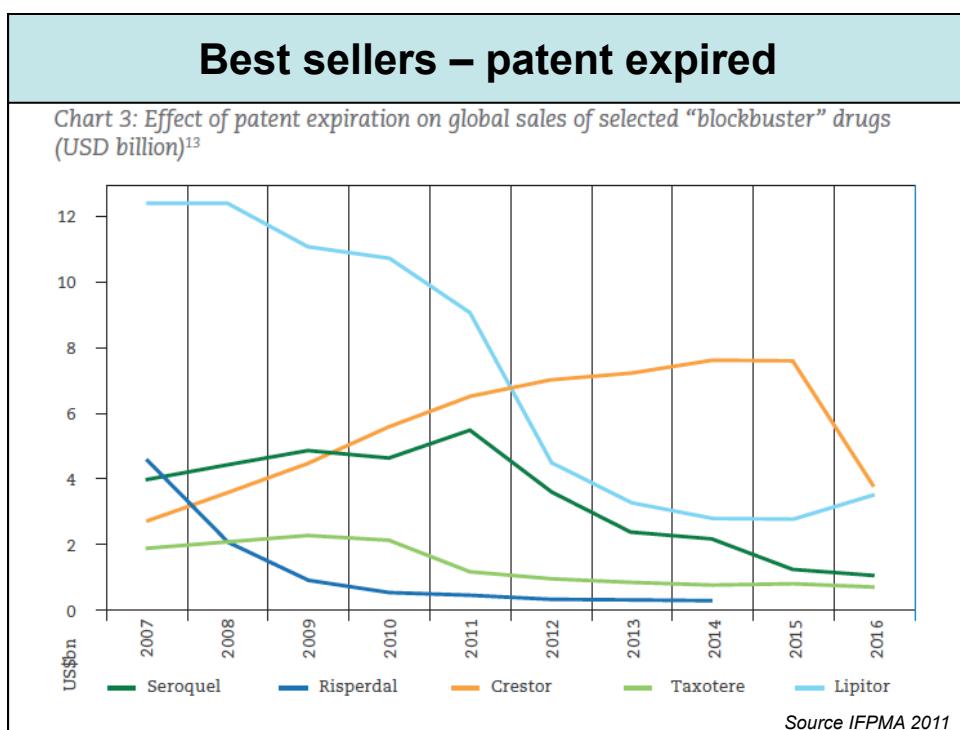
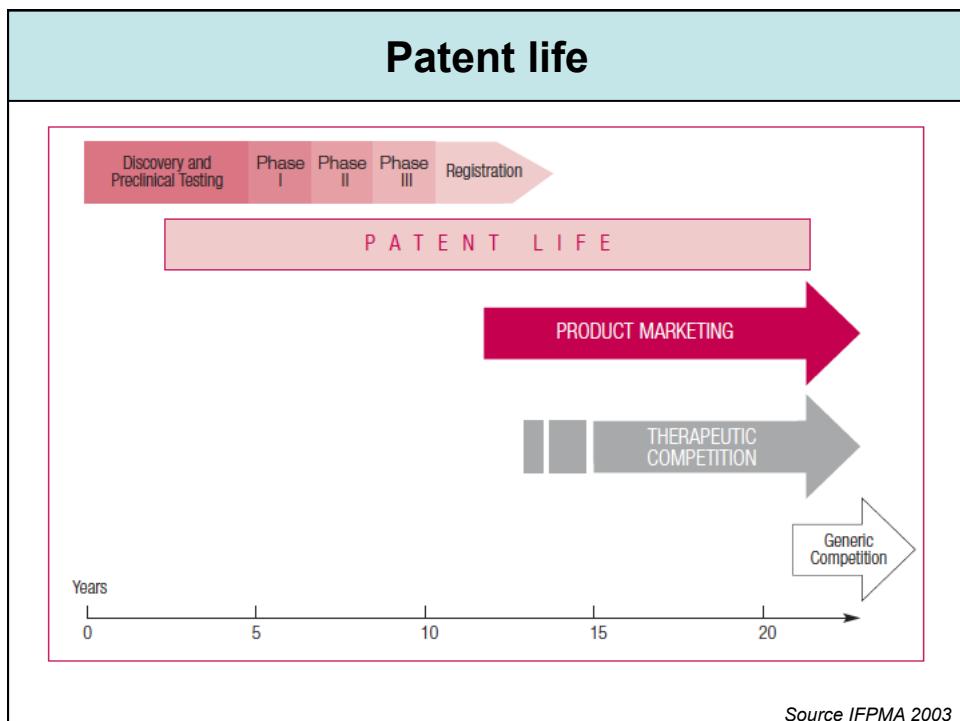
Orphan drug → treatment of orphan disease or rare disease

Orphan disease

- affect small part of population
- severe handicap or fatal prognosis, often early in life (30 % children with orphan disease die before age of 5 years)
- mostly genetic disorder
- e.g. cystic fibrosis
- companies specialized in orphan drug, e.g. Swedish Orphan Biovitrum, Shire, Biomarin, Genzyme

Orphan drug

- may sell without competition for seven years in US and 10 years in EU
- may get clinical trial with alleviated rules
- may benefit of tax incentives



Generic drugs and biosimilars

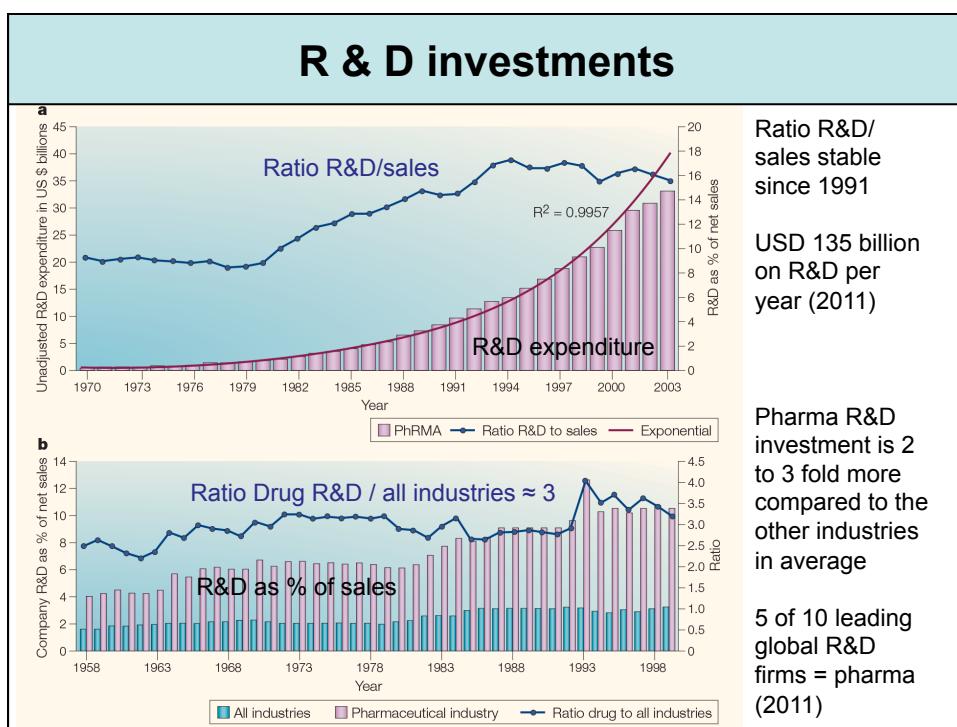
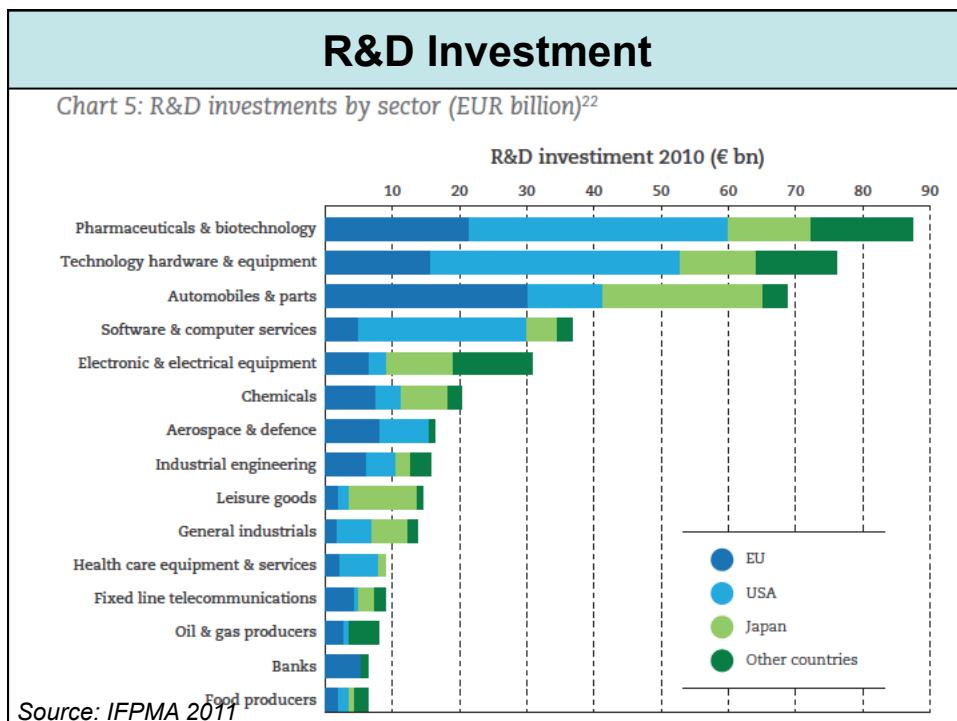
- A **generic drug** is a chemically equivalent drug produced and sold by a different company than the company developing the drug, after the patent protection has expired. It is usually less expensive than the original drug.
- **Biosimilar or generic biopharmaceutical**
 - Supposedly the same drug as the originator drug
 - Same product → 'impossible'
 - Same manufacturing process → 'impossible'
 - Same specifications (quality attributes of the drug) → difficult
 - New clinical trials required

R&D Investment

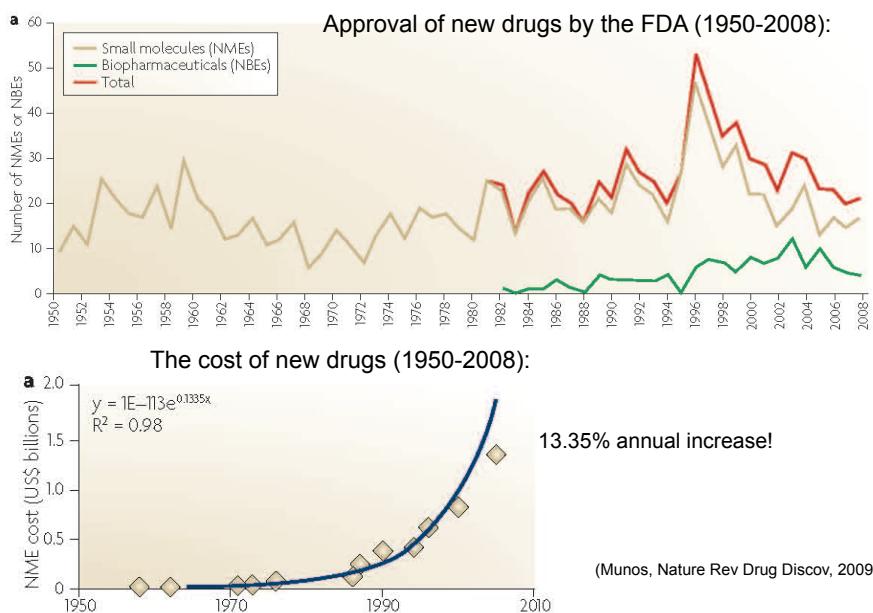
Top 10 Pharmaceutical Companies by R&D Investment
(in 2012, in million €, [2])

Rank	Company	Country	R&D 2012 (€ million)
1	Roche		7,008
2	Novartis		6,923
3	Merck US		5,996
4	Johnson & Johnson		5,809
5	Pfizer		5,740
6	Sanofi-Aventis		4,909
7	GlaxoSmithKline		4,229
8	Eli Lilly		4,000
9	AstraZeneca		3,375
10	Abbott Laboratories		3,276

Source: http://www.chemistryviews.org/details/ezine/6953721/Trends_in_RD_Spending.html

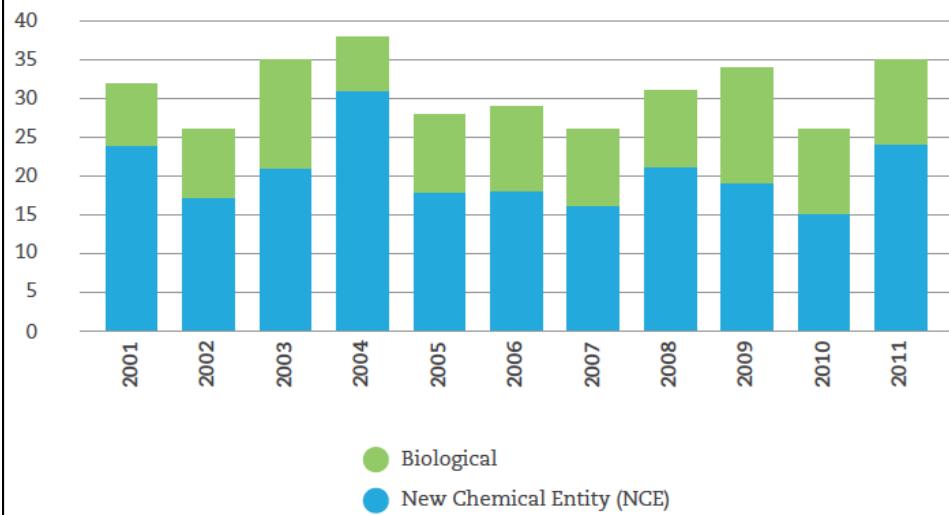


Productivity of the Pharmaceutical Industry



Productivity of the Pharmaceutical Industry

Chart 4: Number of new chemical and biological entities approved by the US Food and Drug Administration, 2001–2011¹⁴

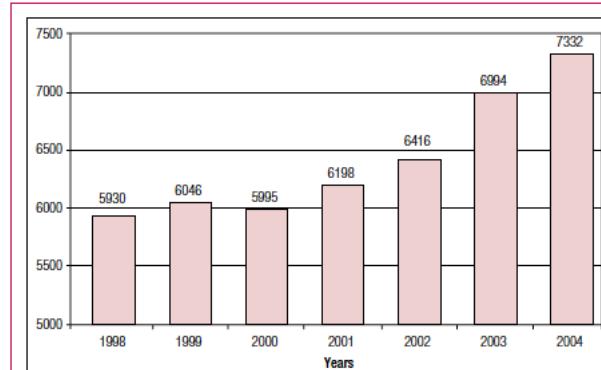


Actual trends

- Actual trends = harvest of low-hanging fruits has already been done
- New drugs are mostly 'me-too's', arising from incremental improvements rather than truly innovation
- Truly innovation mostly government funded
- Growing pipeline

Pipeline =
All the new drugs
in development of a company

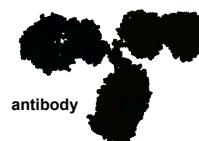
FIGURE 4. GROWING NUMBER OF COMPOUNDS IN THE R&D PIPELINE



Source IFPMA 2003

Trends in the Pharmaceutical Industry

- Protein therapeutics
 - Replacement therapy (endogenous proteins) → END
 - Monoclonal antibodies, derivatives and their fusion proteins
 - More difficult proteins, e.g. orphan drugs
 - Shift from "blockbuster" drugs to specialized drugs
 - Biosimilar
- External partnerships with academia/small biotech
- Purchase of ideas/projects: small companies → higher level of innovation than Big Pharma
- Global Acquisition and reconsolidation
- New types of biologics: Gene therapy, Cell therapy, tissue engineering
- New delivery pathways, i.e. nanoparticles



Lectures: *Gene therapy and Cell Therapy* by Kariem Ahmed + VChotteau – KI & KTH;
Nanoparticles in drug delivery by Lovisa Ringstad – RISE; *Biopolymer* by Thomas Crouzier - KTH

Evolution of the Top Ten Best-Selling Drugs Worldwide 2006	
Trade name	Company
1. Lipitor	Pfizer
2. Plavix	Bristol-Myers Squibb / Sanofi-Aventis
3. Nexium	AstraZeneca
4. Abilify	Otsuka / Bristol-Myers Squibb
5. Advair Diskus	Glaxo SmithKline
6. Seroquel	AstraZeneca
7. Singulair	Merck
8. Crestor	Shionogi / AstraZeneca
9. Cymbalta	Eli Lilly
10. Humira	Abbott
11. Enbrel	Amgen /Wyeth
12. Remicade	Centocor / Schering-Plough /Janssen

Treatment of autoimmune diseases such as rheumatoid arthritis

Evolution of the Top Best-Selling Drugs Worldwide 2012		
rank	product	sales (US\$Bn)
1	Advair Diskus	8.9
2	Humira	8.5
3	Crestor	8.3
4	Nexium	7.5
5	Enbrel	7.5
6	Remicade	7.3
7	Abilify	7.0
8	Lantus	6.6
9	MabThera	6.0
10	Cymbalta	5.8
11	Avastin	5.4
12	Plavix	5.2
13	Spiriva	5.1
14	Liptor	5.1
15	Herceptin	5.0
16	Singulair	4.7
17	Lyrica	4.6
18	Copaxone	4.5
19	Glivec	4.3
20	Neulasta	4.3

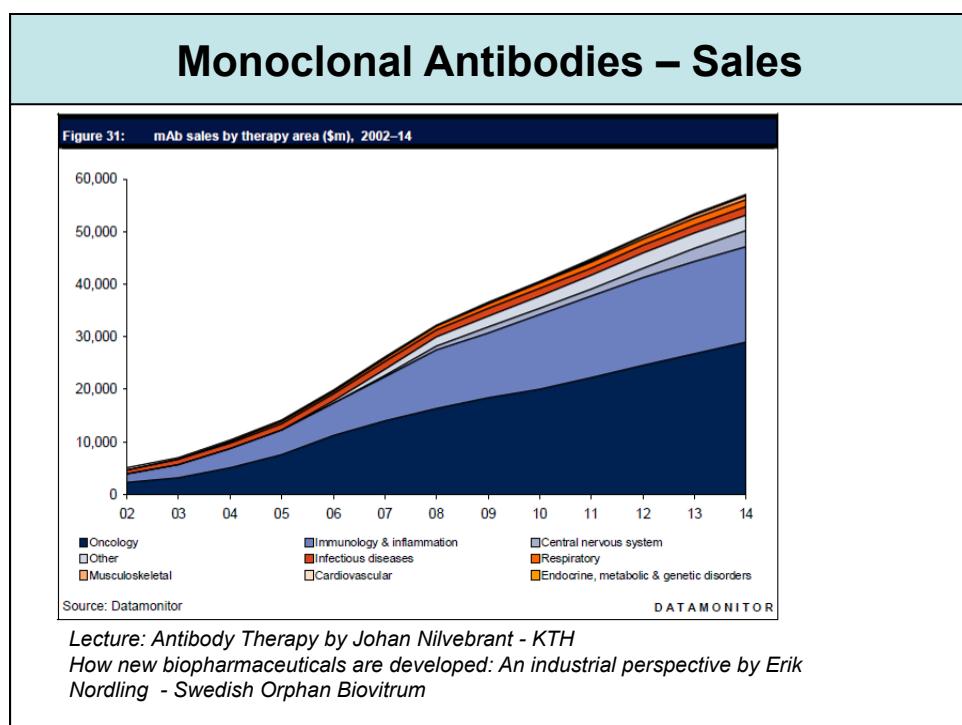
Lindsley C W 2013

Evolution of the Top Best-Selling Drugs Worldwide 2014					
Top 10 drugs 2014 sales (\$m)					
Brand	Indication	Company	2014 sales (\$m)	2020 sales (\$m)	
1 Humira	Autoimmune (various)	AbbVie	12543	14780	
2 Sovaldi	Hepatitis C	Gilead	10283	16621	
3 Remicade	Autoimmune (various)	J&J/Merck & Co.	9240	7601	
4 Enbrel	Autoimmune (various)	Amgen/Pfizer	8538	7754	
5 Lantus	Diabetes	Sanofi	8433	5497	
6 Rituxan	Leukaemia/lymphoma	Roche	7550	5486	
7 Avastin	Cancer (various)	Roche	7021	6480	
8 Advair	Asthma/COPD	GSK	6971	2582	
9 Herceptin	HER2+ breast cancer	Roche	6866	4573	
10 Januvia	Diabetes	Merck & Co.	6002	9187	

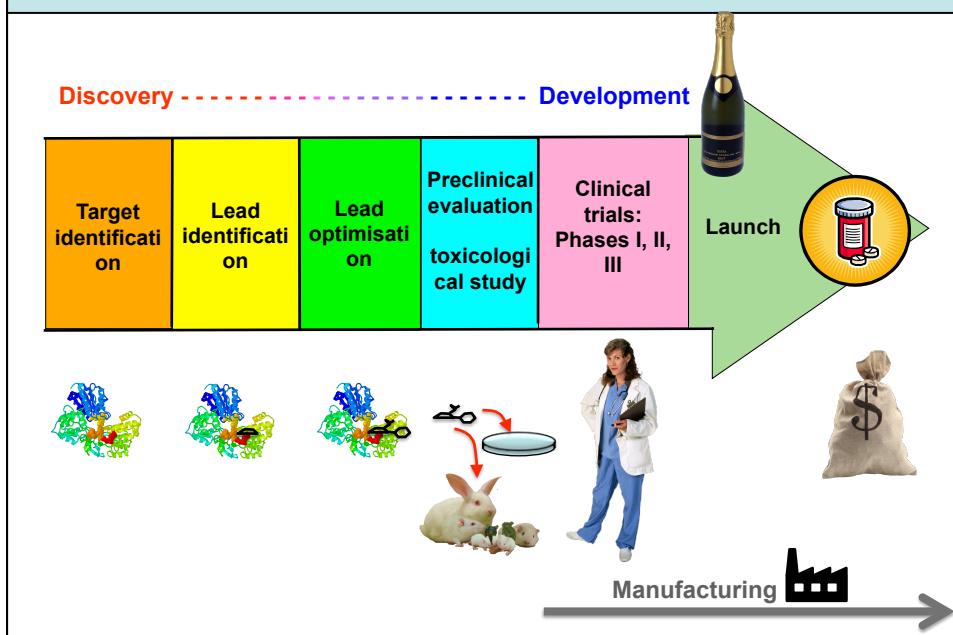
Source: Company reported data; Bloomberg <http://www.firstwordpharma.com/node/1263906#axzz3qXSmCs2y>

Biopharmaceuticals

Small molecules Lecture: Biopharmaceuticals by Patrik Strömberg - Swedish Orphan Biovitrum

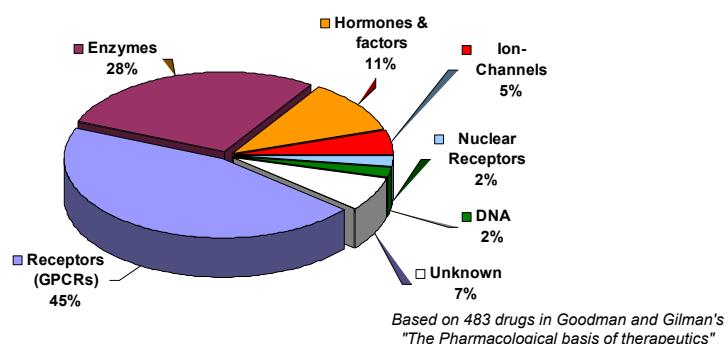


The Process of Drug Discovery / Development



Drug Targets

- The majority of all drug targets are proteins:

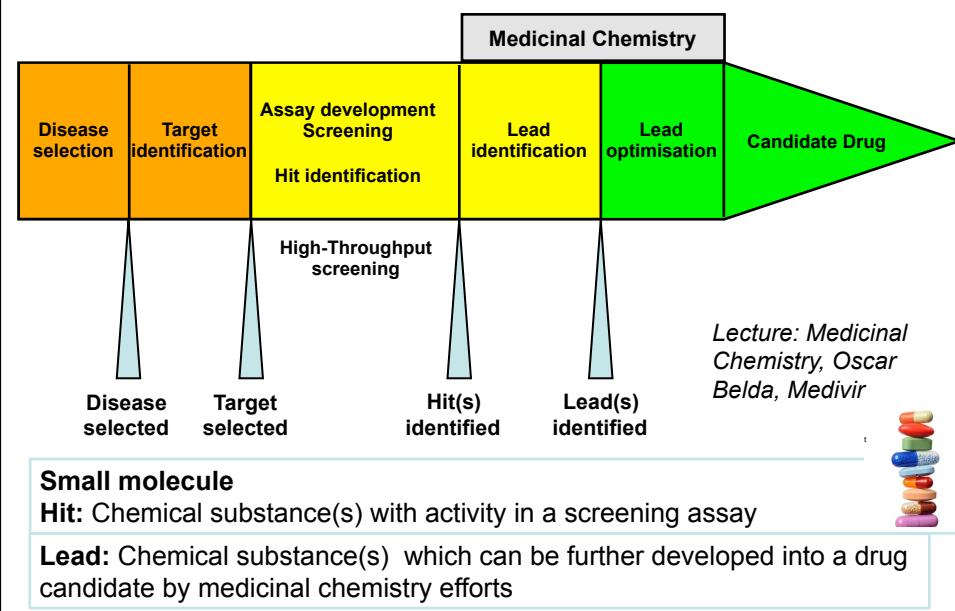


- Many drugs act on several molecular targets
- Estimated that the drugs currently in use act on a total of 324 targets

from: *Nature Reviews Drug Discovery* 5, 993 (2006)

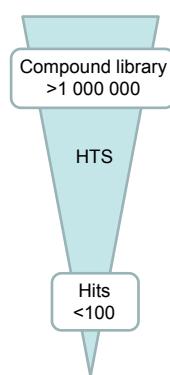
Lecture: Target Validation in Drug Discovery, David Malinowsky

The First Phase: Discovery



In Vitro Screening

- A **screening assay** is a method to measure biological effects of chemical compounds
- Used to rank a collection of chemical compounds for their possible utility as medicines
- The assay can be biochemical, cellular, in vitro, in vivo, homogenous, heterogenous...
- In **high-throughput screening (HTS)**, >20,000 data points/day are generated



Hit: Chemical substance(s) with activity in a screening assay

Lead Generation and optimization

Lead generation

Lead: Chemical substance(s) which can be further developed into a drug candidate by medicinal chemistry efforts

→ Optimization of compounds from the initial screen

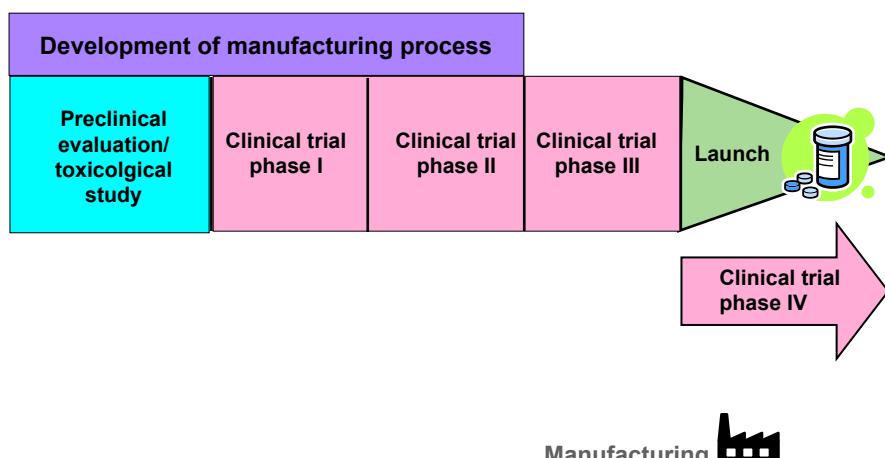
- Factors to consider:

- Potency
- Synthesis (simple chemistry?)
- IPR
- Molecular weight, stability, solubility, ...

Lead optimization: synthetic modification of a biologically active compound to fulfil all physicochemical, pharmacokinetic, pharmacological and toxicologic requirements for clinical usefulness

→ generates candidate drug (CD) to be evaluated in preclinical studies

The Second Phase: Development



Development of production process or manufacturing

Small molecule drug

- Synthetic / organic synthesis → process for large scale with importance of efficiency and green aspects
- Formulation and delivery

Biopharmaceuticals

- Recombinant technology
 - Cell expression – Culture – Purification – Formulation and delivery

Lectures:

From Flask to Factory - Design and development of viable and sustainable chemical processes in the pharmaceutical industry – concepts, challenges, goals, Hans-Jürgen Federsel, AstraZeneca

Biopharmaceutical production process development and manufacturing, V Chotteaum Formulation, Thomas Österberg, previously Pfizer

Questions Addressed in Preclinical Studies

- Biological effect?
- How much of the drug is adsorbed?
- How is the drug distributed in the body?
- How long does the substance stay in the body?
- How is the drug metabolized?
- How is the drug excreted from the body?
- What is the therapeutic dose?
- What are the side effects?
- At what dose are side effects noticed?



ADME: Absorption, Distribution, Metabolism, Excretion

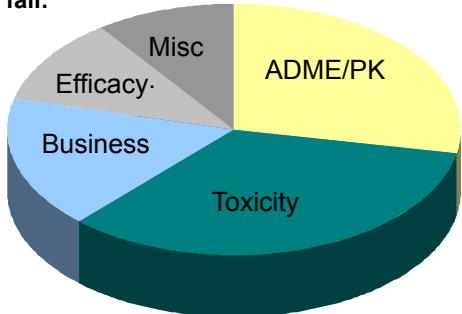
Pharmacodynamics: What the drug does to the body

Pharmacokinetics: What the body does to the drug

Lectures: Preclinical Development, Edis Travancic, Swedish Orphan Biovitrum; Toxicology and Safety Assessment in Drug Discovery and Drug Development Charlotte Nilsson, Swetox

Preclinical Evaluation

Why drugs fail:



Preclinical evaluation of a drug candidate is extremely important since favorable ADME, pharmacokinetics and toxicity profiles are critical for its success in the clinical trials!

Toxicological Testing

Reasons for toxicological testing:

- Assist in the selection of drug candidates
 - potency, selectivity
 - favorable pharmacokinetic and metabolic properties
 - low toxicity
- Risk assessment
 - identification and characterization of possible side effects
- Support for the clinical trials

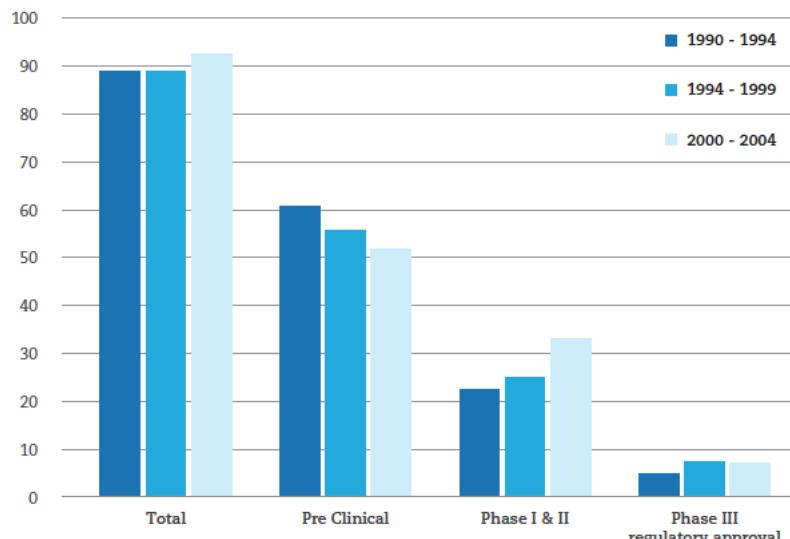


Toxicological testing is required before clinical trials can be performed and a new drug can be approved

Lecture: Toxicology and Safety Assessment in Drug Discovery and Drug Development, Charlotte Nilsson, Swetox

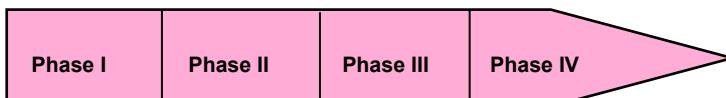
Failure rates

Chart 1: Pharmaceutical R&D Failure Rates⁶



Source IFPMA 2011

Clinical Trials

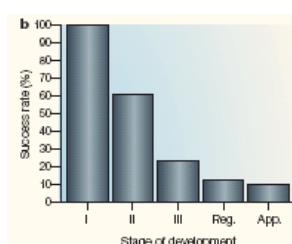


Phase I: Human Pharmacology, First-in-Human (FIH), Maximum Tolerated Dose

Phase II: Therapeutic Exploratory, Proof-of-Concept (POC), Dose-finding

Phase III: Therapeutic Confirmatory

Phase IV: Therapeutic Use



From: Nature Drug Discovery Reviews (2004) 3; 711

Only 1 in 10 drug candidates entering in clinical trials is successful!

Lecture: Clinical Trials, An van Es-Johansson, Swedish Orphan Biovitrum

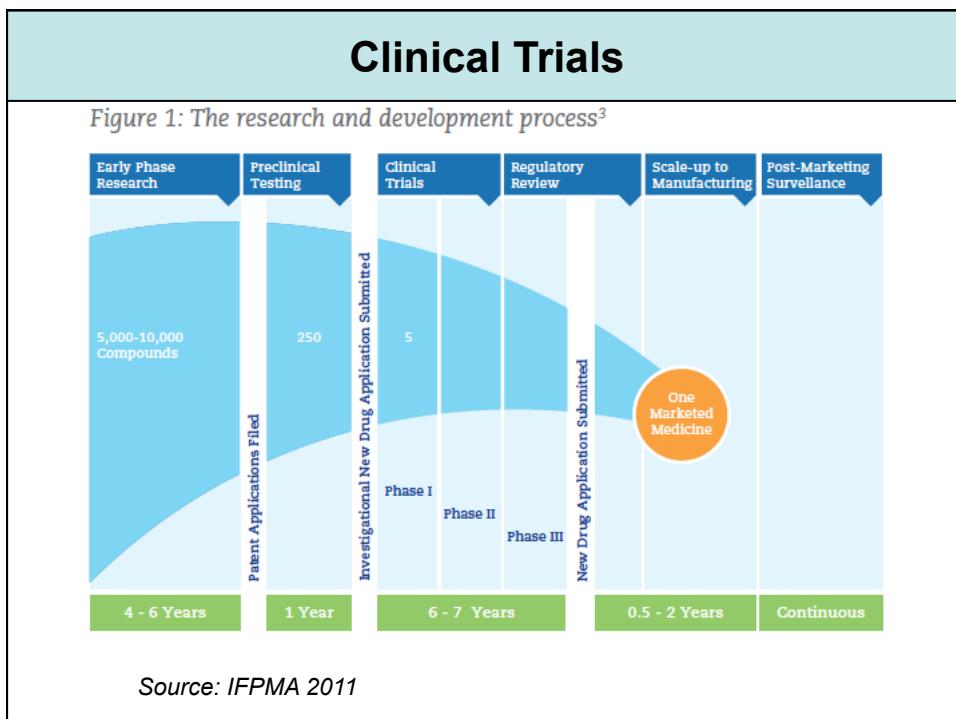


FIGURE 5. PROCESS OF PHARMACEUTICAL R&D

Clinical Trials

R&D Stage	Research & Discovery	Preclinical development	Phase I	Phase II	Phase III	Registration	Phase IV
Main Activities	Drawing on basic exploratory research to identify targets, initial research on new compounds is carried out in the laboratory (high throughput screening, lead identification and optimization) to select the most promising compounds.	Selected compounds are studied in animals under Good Laboratory Practice for toxicity and safety; in parallel, specific analytical methods are developed for further development.	Successful compounds are then tested in humans in 3 phases of clinical trials: <ul style="list-style-type: none"> Phase I – safety 120 and tolerability in healthy volunteers Phase II – safety, efficacy and bioequivalence studies in small groups of patients Phase III – large trials with different populations to demonstrate proof of efficacy, safety and value 	If the results of clinical trials are satisfactory in terms of quality, efficacy and safety, a regulatory dossier is presented to the regulatory authorities for approval.	Post-marketing studies involving thousands of patients are initiated after the launch of the medicine, to identify any previously unforeseen side effects.		
Success Rate*	Less than 1 %	70 %	50 %	50 %	90 %	N.A.	
Time	4-6 years	1 year	1-1.5 years	1-2 years	2-3 years	1-2 years	Several years

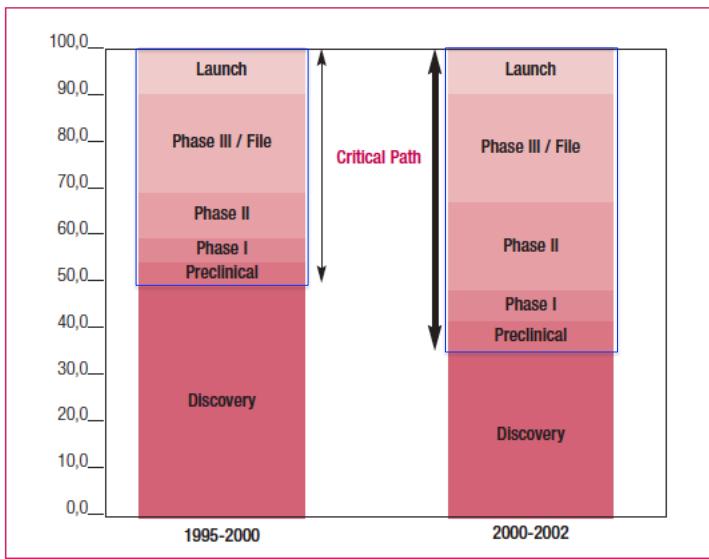
* Success rates reflect the number of drug candidates that successfully pass through to the next R&D stage.

- Increasing late stage failures due to more stringent regulators Phase III failures (e.g. failure 30 % → 50 % in 2000: FDA asking for additional data) → more expensive

Source IFPMA 2003

FIGURE 6. THE ESCALATION OF DEVELOPMENT COSTS
COST ELEMENTS OF R&D PROCESS AS A PERCENTAGE OF TOTAL COSTS

Clinical Trials



Increasing cost in clinical testing: today, drugs are more complex → need better evidence of safety and efficacy → more patients and longer tests

'critical path' = part of R&D process, from selection of a candidate product for development, includes preclinical and clinical studies

Source IFPMA 2003

The Regulation of Drug Development

Medical Products Agency (= Läkemedelsverket)

The Medical Products Agency is the Swedish national authority responsible for regulation and surveillance of the development, manufacturing and sale of drugs and other medicinal products.



web page: www.mpa.se



FDA: US Food and Drug Administration



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA: European Medicines Agency

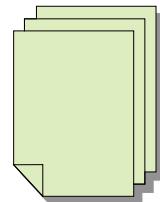
Quality Assurance

Nearly every step in the process of drug development, from drug candidate to product to the market, is regulated by authorities to ensure patient safety and drug efficacy

GLP = Good Laboratory Practices

GCP = Good Clinical Practices

GMP = Good Manufacturing Practices



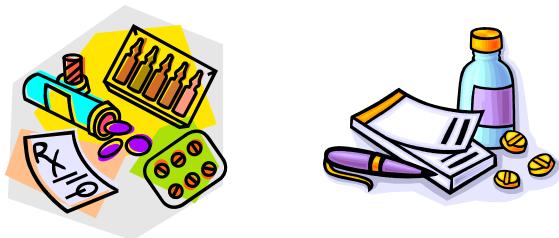
Key aspects of GMP

- manufacturing, testing, quality assurance → safety for human use
- manufacturing in clean and hygienic manner
- controlled conditions (process, raw material, analyses, release)
- reproducibility, robustness, process validation for compliance of specifications, changes strictly controlled
- traceability (e.g. all raw materials, cell line)
- documentation (clear, unambiguous, information fully recorded, no cross-contamination)
- established quality control system

Why Are the Regulations So Strict?

The handling of drugs is strictly regulated because

- There are both desired effects and side-effects of a drug
- The user is not able to deem the quality and risk of the drug
 - No access to the information
 - No knowledge to treat this information
- Several severe accidents have occurred



Names of Drugs

Small molecule drugs

Trade name: The brand name the company uses when selling the drug
e.g. Lipitor (Pfizer)



Generic name: A name given to the drug when developed by the company e.g. atorvastatin (= Lipitor)

Chemical name: The systematic name of the substance according to IUPAC nomenclature

e.g. [R- (R*,R*)]-2-(4-D-fluorophenyl)-beta-Δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid

Biopharmaceuticals (complicated)

- Primary protein sequence (e.g. Ala-Tyr-Ser-Glu-Gly- - - -)
- Trivial names (e.g. α-amylase)
- Manufacturing process (culture/fermentation and purification) are part of the definition of the drug protein
- Potential variants: glycosylation, disulfide bridges, monomer/multimer states, etc.



Lectures

Introduction by Véronique Chotteau from KTH

Pharmacology I by Sabina Devillers from Karolinska Institutet

Intellectual Property Rights (IPR) by Hampus Rystedt from ZACCO

Pharmacology II by Sabina Devillers from Karolinska Institutet

Pharmacology III by Sabina Devillers from Karolinska Institutet

Biopharmaceuticals by Patrik Strömberg from Swedish Orphan Biovitrum

Target Validation in Drug Discovery by David Malinowsky from Sybicon

Medicinal Chemistry by Oscar Belda from Medivir

How new biopharmaceuticals are developed: An industrial perspective by Erik Nordling from Swedish Orphan Biovitrum

Antibody Therapy by Johan Nilvebrant from KTH

Toxicology and Safety Assessment in Drug Discovery and Drug Development by Charlotte Nilsson from Swetox

Preclinical Development by Edis Travancic from Swedish Orphan Biovitrum

Biopharmaceutical production process development and manufacturing by Véronique Chotteau from KTH

Design and development of viable and sustainable chemical processes in the pharmaceutical industry – concepts, challenges, goals by Hans-Jürgen Federsel from EnginZyme

Clinical Trials by An van Es-Johansson from Swedish Orphan Biovitrum

Formulation by Thomas Österberg from Pfizer

Commercialising Science Innovation and Entrepreneurship by Eugen Steiner from Health Cap

Nanoparticles in drug delivery by Lovisa Ringstad from RISE

Cell Therapy, gene therapy, vaccine by Kariem Ahmed + VChotteau from Karolinska Institutet & KTH

Biopolymer-based materials for biomedical applications by Thomas Crouzier from KTH